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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,055	09/27/2005	Ralph Biemans	B45309	6847

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EXAMINER	
GANGLE, BRIAN J	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
08/07/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/523,055	BIEMANS ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,20-36 and 38-60* is/are pending in the application.

4a) Of the above claim(s) *3,5-17,25-36,39-42 and 44-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,20-24,38 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2/2005;4/8/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group IX in the reply filed on 4/8/2008 is acknowledged. The traversal is on the ground(s) that claims 4 and 20-27 should be included in Group IX because they depend from and require all of the limitations of the elected claims. Applicants additionally request examination of amended claims 45-48, as these are now directed to L3 LOS rather than L2 LOS. This is found partially persuasive. As amended, claims 4, 20-24 read on elected Group IX and are rejoined. Claims 25-27 do not read upon the elected invention as they include alteration of lgtG. Claims 45-48 are drawn to a process of growing a high cell density of an L3 strain and do not include all of the limitations of claim 1.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-17, 20-36, and 38-60 are pending. Claims 3, 5-17, 25-36, 39-42, 44-60 are withdrawn as being drawn to nonelected inventions. Claims 1-2, 4, 20-24, 38, and 43 are currently under examination.

Information Disclosure Statement

The information disclosure statements filed on 2/2/2005 and 4/8/2008 have been considered. Initialed copies are enclosed. The reference by Zakirov *et al.* has not been considered as no English language translation was available.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4, 20-24, 38, and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite by the phrase "LOS oligosaccharide synthesis gene is modified to render the expression of the gene less phase variable." It is not clear what

the expression of the gene is to be compared to so that one can determine whether it is "less phase variable." This could refer to making the strain less variable than it was, or to making the strain less variable than other strains. In addition, it is not clear how one could "render the expression of the gene less phase variable." It appears, from the art and the specification, that reducing the length of the homopolymeric G tract would reduce the likelihood of a frameshift mutation, thus rendering the strain less phase variable. However, claims 20-24 require "fixing" of lgtA expression (which is the same as rendering the gene non-phase variable) by reducing the length of the homopolymeric tract. If simply reducing the length renders the strain non-phase variable, then how does one make it less phase variable? Conversely, if merely reducing the length of the homopolymeric tract only renders the strain less phase variable, then how does one render it non-phase variable? This rejection affects dependent claims.

Claims 20 and 23 are rendered vague and indefinite by the phrase "an lgtA gene product." The use of the word "an" implies that there is more than one lgtA gene product. It is not clear what products lgtA makes beside a single glycosyltransferase. This rejection affects dependent claims

Claim 43 is vague and indefinite because it is dependent on a cancelled claim. As such, the claim is incomplete and one cannot determine the metes and bounds of the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4, 20-24, 38, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jennings *et al.* (Infect. Immun., 43:407-412, 1984, referred to hereafter as Jennings-1984) in view of Jennings *et al.* (Microbiol., 145:3013-3021, 1999, IDS filed 2/2/2005, referred to hereafter as Jennings-1999).

The instant claims are drawn to methods of isolating L3 LOS comprising (a) selecting a neisserial strain with phase-variable L3 LOS synthesis, (b) genetically engineering the strain so that the homopolymeric nucleotide tract of a phase variable lgtA gene is modified to render the expression of the gene less phase variable, and (c) isolating L3 LOS from the strain (claim 1); where in the gene is modified to render expression of the gene non-phase variable (claim 2); wherein the neisserial strain is a meningococcal strain or a meningococcus B strain (claim 4); wherein step b) comprises the step of fixing the expression of an IgtA gene product (claim 20); wherein the expression of the IgtA gene product is fixed by reducing the length of the homopolymeric nucleotide tract within the open-reading frame of the gene and maintaining the open-reading frame in frame (claim 21); wherein the homopolymeric G tract in the IgtA open-reading frame is reduced to 8, 5 or 2 consecutive G nucleotides (claim 22); wherein the expression of an IgtA gene product is fixed by changing the sequence of the homopolymeric G nucleotide tract within the open-reading frame of the IgtA gene such that one or more GGG codons encoding Glycine is changed to any other codon encoding glycine, or a codon encoding a conservative mutation, or the TCG codon encoding Serine is changed to any other codon encoding Serine, or a codon encoding a conservative mutation and maintaining the open-reading frame of the gene in frame (claim 23); wherein 2, 3 or 4 codons in the homopolymeric tract are changed and encode the identical amino acid or a different amino acid (claim 24); further comprising the step of conjugating the L3 LOS to a carrier comprising a source of T-cell epitopes or the step of presenting the L3 LOS in a liposome formulation (claim 38); and a process of making an immunogenic composition comprising the steps of producing isolated L3 LOS by the process of claim 37 and formulating the L3 LOS with a pharmaceutically acceptable excipient (claim 43). It is noted that claim 43 is dependent on a cancelled claim. For the purposes of art rejections, claim 43 is being interpreted as being dependent upon claim 1.

Jennings-1984 disclose a method of isolating L3 LOS from *Neisseria meningitidis* group B where cells are grown and LPS (which is the equivalent of LOS) is isolated (page 407, column 2). The LPS is conjugated to tetanus toxoid and dissolved in phosphate-buffered saline (page 408, column 1, paragraphs 2-4).

Jennings-1984 differs from the instant invention in that they do not disclose genetically engineering the strain so that the homopolymeric nucleotide tract of a phase variable lgtA gene is modified to render the expression of the gene less phase variable.

Jennings-1999 disclose the genetic basis of the phase variation in the LPS genes of *Neisseria meningitidis*. Jennings-1999 show that this phase variation occurs because of frameshift mutations that occur in a homopolymeric tract of G residues in the lgtA gene. When in-frame, lgtA is expressed and when out-of-frame, lgtA is not expressed resulting in a loss of the L3 immunotype (page 3017, column 2). Jennings-1999 also show that strains with phase variation generally have 14 G residues in this tract, while strains with only 5 G residues lack phase variation (page 3017, column 2).

It would have been obvious to one of ordinary skill in the art, at the time of invention, to reduce the homopolymeric G tract of lgtA to 5 G residues, using well known techniques, in order to reduce or eliminate phase variation based on the teachings of Jennings-1999. Genetic manipulation was well known and one could have reduced the homopolymeric tract either by eliminating residues or by changing the residues to any suitable codon; this would simply be a design choice.

One would have had a reasonable expectation of success because the means by which phase variation occurs is disclosed by Jennings-1999 and the genetic techniques required to make the necessary modifications were well known in the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian J Gangle/
Examiner, Art Unit 1645

/Shanon A. Foley/
Supervisory Patent Examiner, Art Unit 1645